# Advances in Deceased Donor Liver Transplantation

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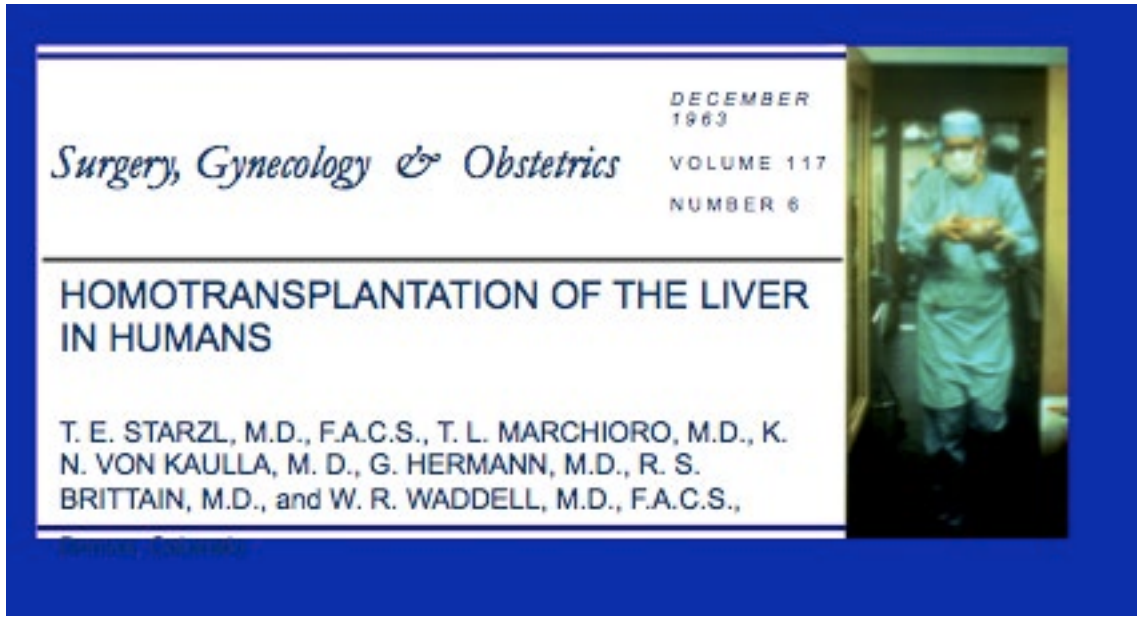
# Disclosures

- Chair, OPTN Liver & Intestine Committee

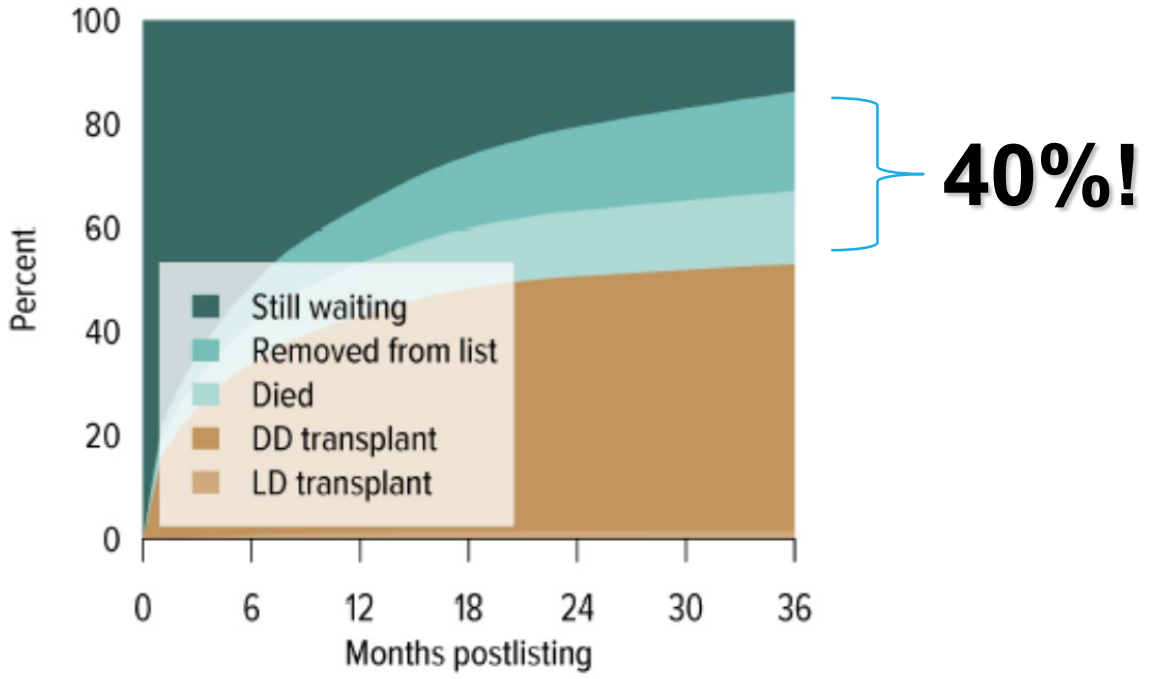
  This presentation reflects my opinions and not that of the OPTN or UNOS

# 1963:
# Worlds First Attempts at Liver Transplantation




| Age | Date | City | Diagnosis | Survival (Days) |
|---|---|---|---|---|
| 3 | 03/63 | Denver | Biliary Atresia | 0 |
| 48 | 05/63 | Denver | Hepatoma w/Cirrhosis | 22 |
| 68 | 06/63 | Denver | Duct Cell Carcinoma | 7.5 |
| 52 | 07/63 | Denver | Hepatoma w/Cirrhosis | 6.5 |
| 58 | 09/63 | Boston | Colon Metastases | 11 |
| 29 | 10/63 | Denver | Hepatoma | 23 |
| 75 | 01/64 | Paris | Colon Metastases | 0 |

# Deaths on Liver Transplant Wait List

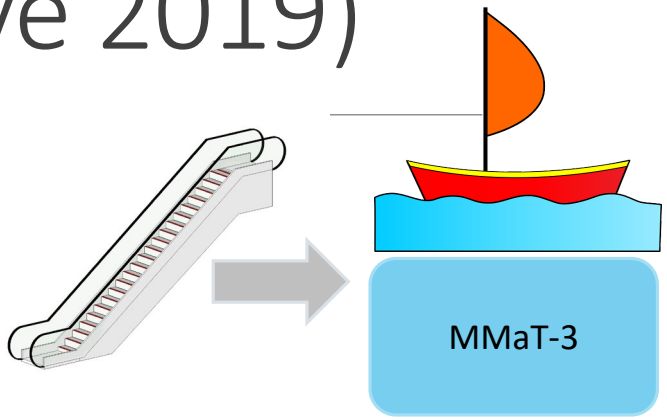


# Outline

- MELD exceptions
- Allocation of Liver DD Grafts
- Improving Extended Criteria Donors (NMP and NRP, Other)

# MELD Exceptions

# Changes to MELD exceptions (effective 2019)




No longer a q 3 month MELD escalator

MELD scores provided for standard exceptions are based on Median MELD at Transplant (MMaT)

MMaT is calculated for *geographic areas every 180 days

*Around donor hospital (previously was around transplant center)

Most adult exception scores are MMaT-3

Most Peds exceptions scores are MMaT

# Standard MELD/PELD Exceptions

| Diagnosis | Adult Score | Adolescent Score | Pediatric Score |
|---|---|---|---|
| CCA | MMaT-3 | MMaT | MPaT |
| CF | MMaT-3 | MMaT | MPaT |
| FAP | MMaT-3 | MMaT | MPaT |
| HAT (in not Status1 A/B) | MELD 40 | N/A | N/A |
| HPS | MMaT-3 | MMaT | MPaT |
| Metabolic Disease | N/A | MMaT | MPaT |
| POPH | MMaT-3 | MMaT | MPaT |
| Primary Hyperoxaluria | MMaT | MMaT+3 | MPaT+3 |
| HCC | MMaT-3 after 6 month delay | MELD 40 | PELD 40 |

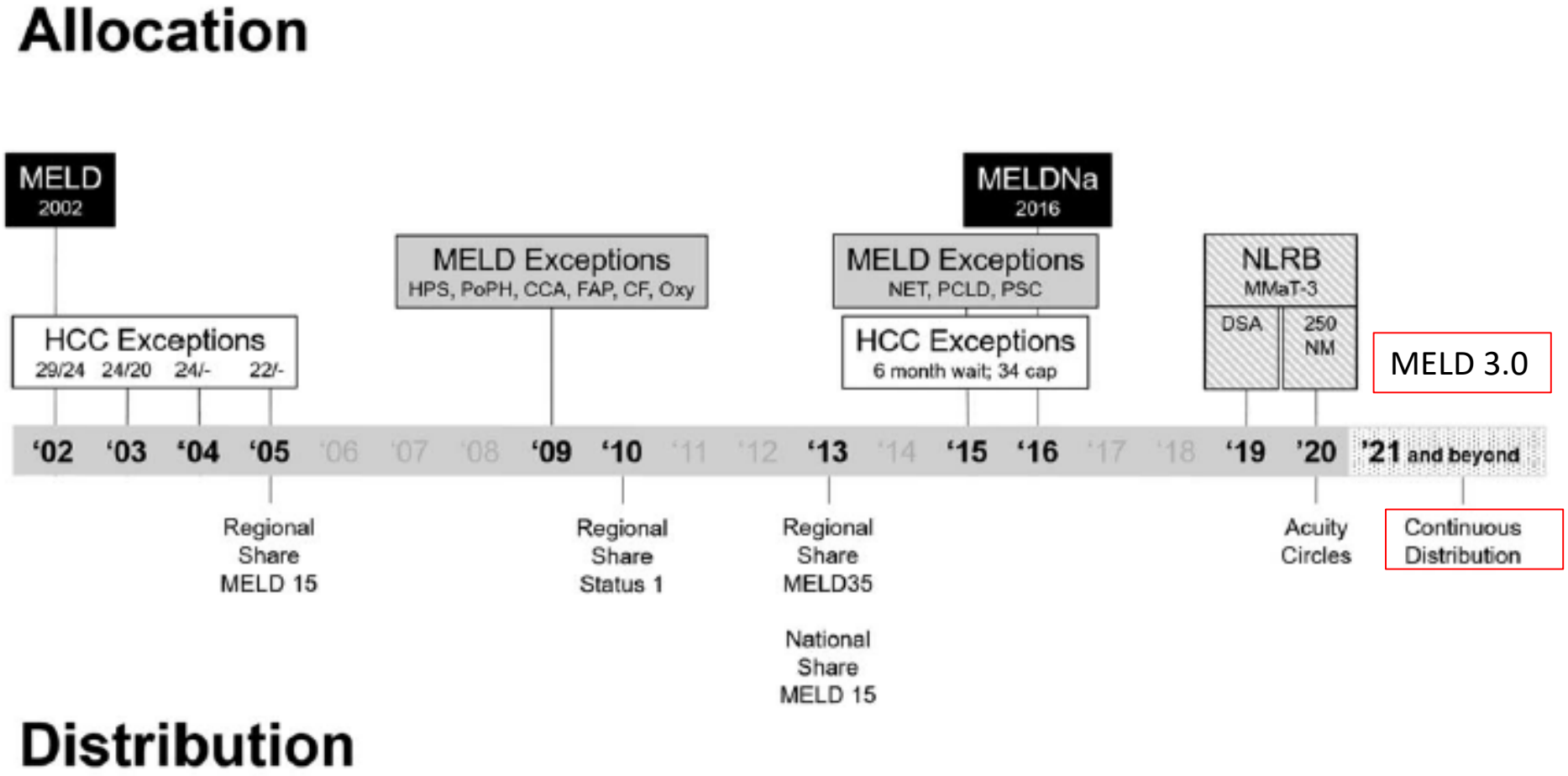
# Adult Transplant Oncology NLRB Guidance - *NEW*

| Diagnosis | Purpose | Score Recommendation |
|---|---|---|
| **Unresectable Colorectal Liver Metastases** | Emerging literature indicates benefit from transplant, however low calculated MELD scores do not provide sufficient access to transplant | MMaT – 20 |
| **Unresectable Intrahepatic Cholangiocarcinoma and mixed HCC cholangiocarcinoma ≤ 3 cm** | Emerging literature indicates benefit from transplant, however low calculated MELD scores do not provide sufficient access to transplant | MMaT – 3 |
| **Unresectable Downstaged Intrahepatic Cholangiocarcinoma** | There is inadequate evidence to support granting a MELD exception for unresectable downstaged intrahepatic cholangiocarcinoma in adult candidates. | N/A |

*Note: If a candidate's exception score relative to MMaT or MPaT would be lower than 15, the candidate's exception score will be 15.*

# Allocation of DD Livers

# Changes in LT Allocation & Distribution

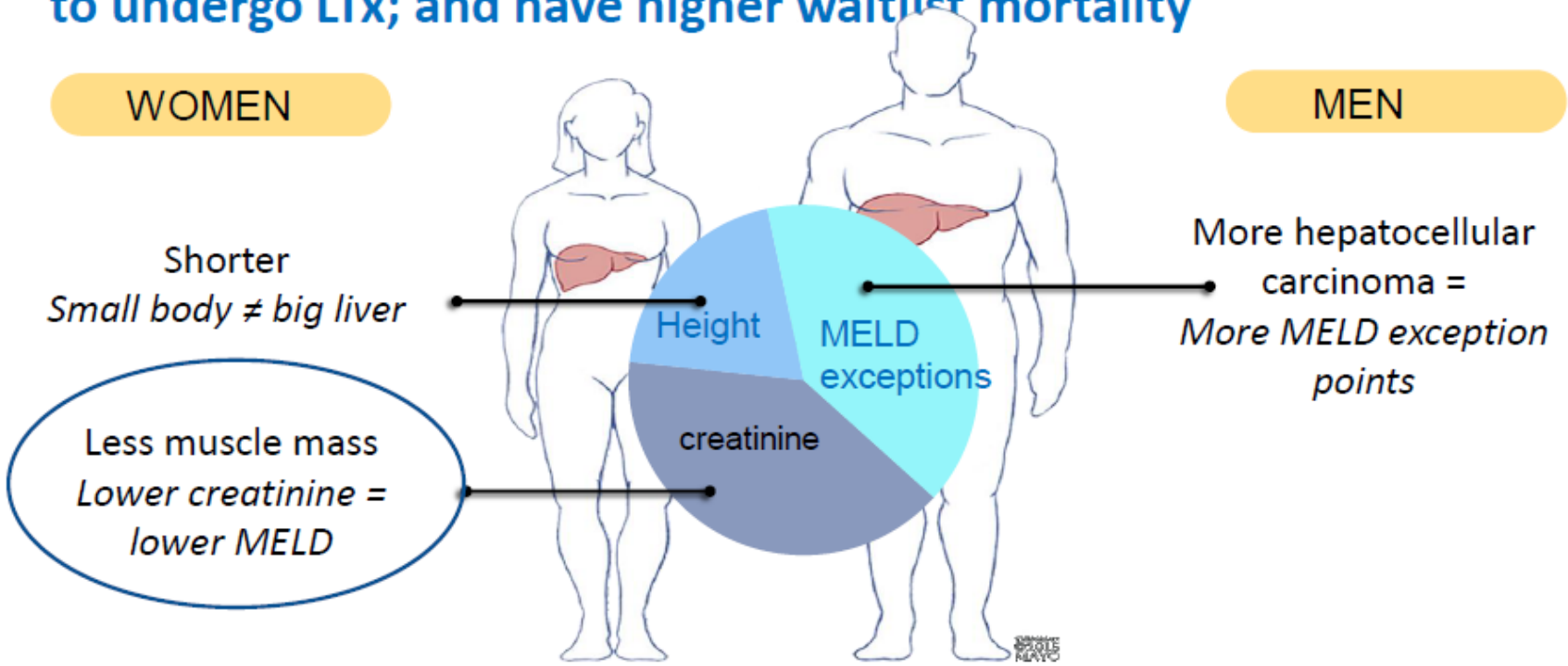


# Access: MELD 3.0

## IMPROVED ACCESS FOR WOMEN AND MALNOURISHED

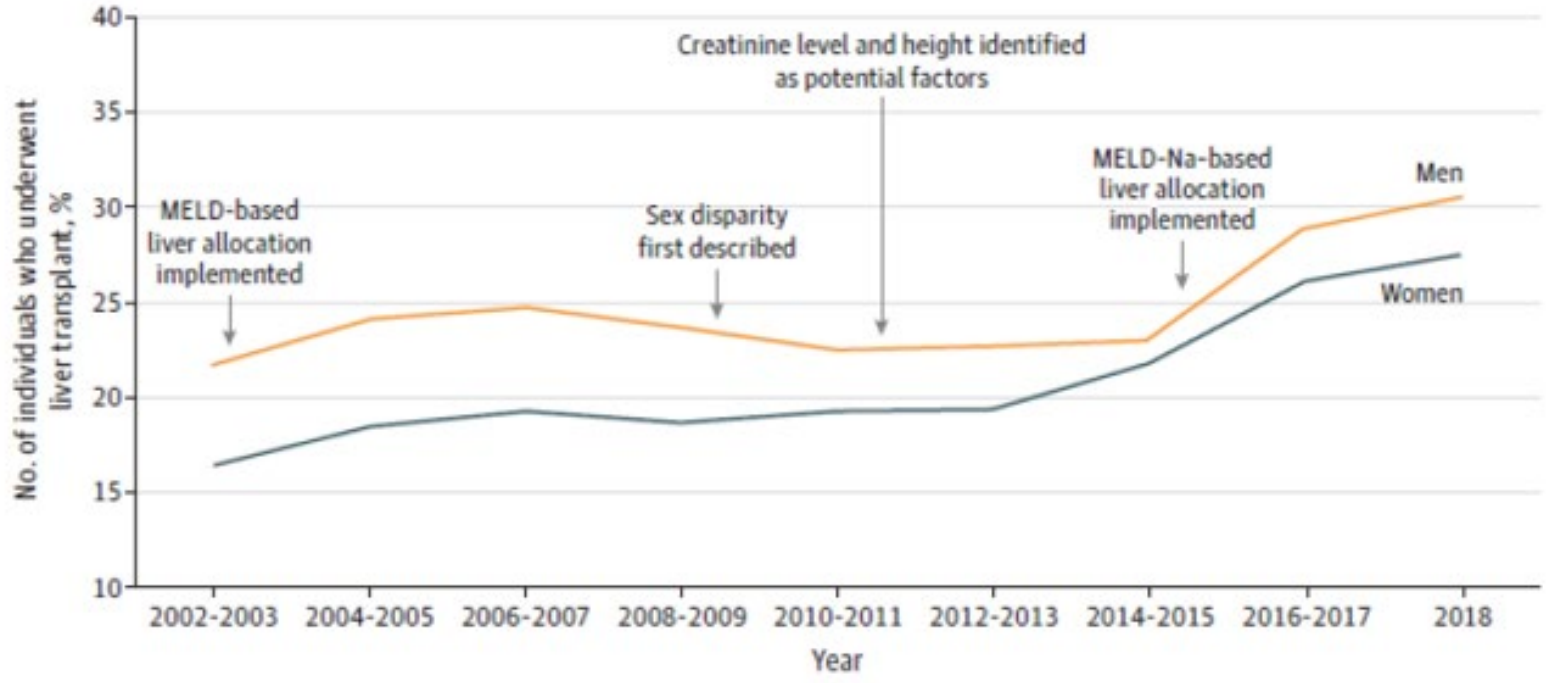
# Women/Shorter Disadvantaged by MELD

**Controlling for age, MELD, Region-- Women are 20% less likely to undergo LTx; and have higher waitlist mortality**



# Women/Shorter Disadvantaged by MELD

**Figure. Proportion of Women and Men Who Underwent Deceased Donor Liver Transplant and Timeline of Important Events in Liver Transplant**




Potential Fix

**MELD 3.0**

= Female, TB, Na, INR, Cre, Albumin

[~+1.3 point for Females]

Lai JAMA Surgery 2020

Kim Hepatology 2020

# MELD 3.0 (July 13,2023)

**MELD 3.0** = 1.33 (if female) + 4.56*$log_e$(bilirubin) + 0.82*(137-Na) + 9.09*$log_e$(INR) + 11.14*$log_e$(creatinine) + 1.85*(3.5-albumin) – 0.24*(137-Na)*$log_e$(bilirubin) – 1.83*(3.5-albumin)*$log_e$(creatinine) + 6

**Bounds for variables:**

Cre: 1 and 3

Na:  125 and 137

Albumin: 1.5 and 3.5

**Effect of interaction terms:**

Low Albumin: smaller effect at higher cre

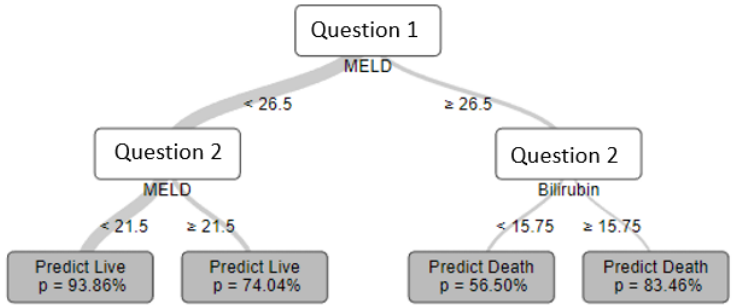
Low Na: smaller effect at higher bilirubin

# Machine Learning: OPOM Variables

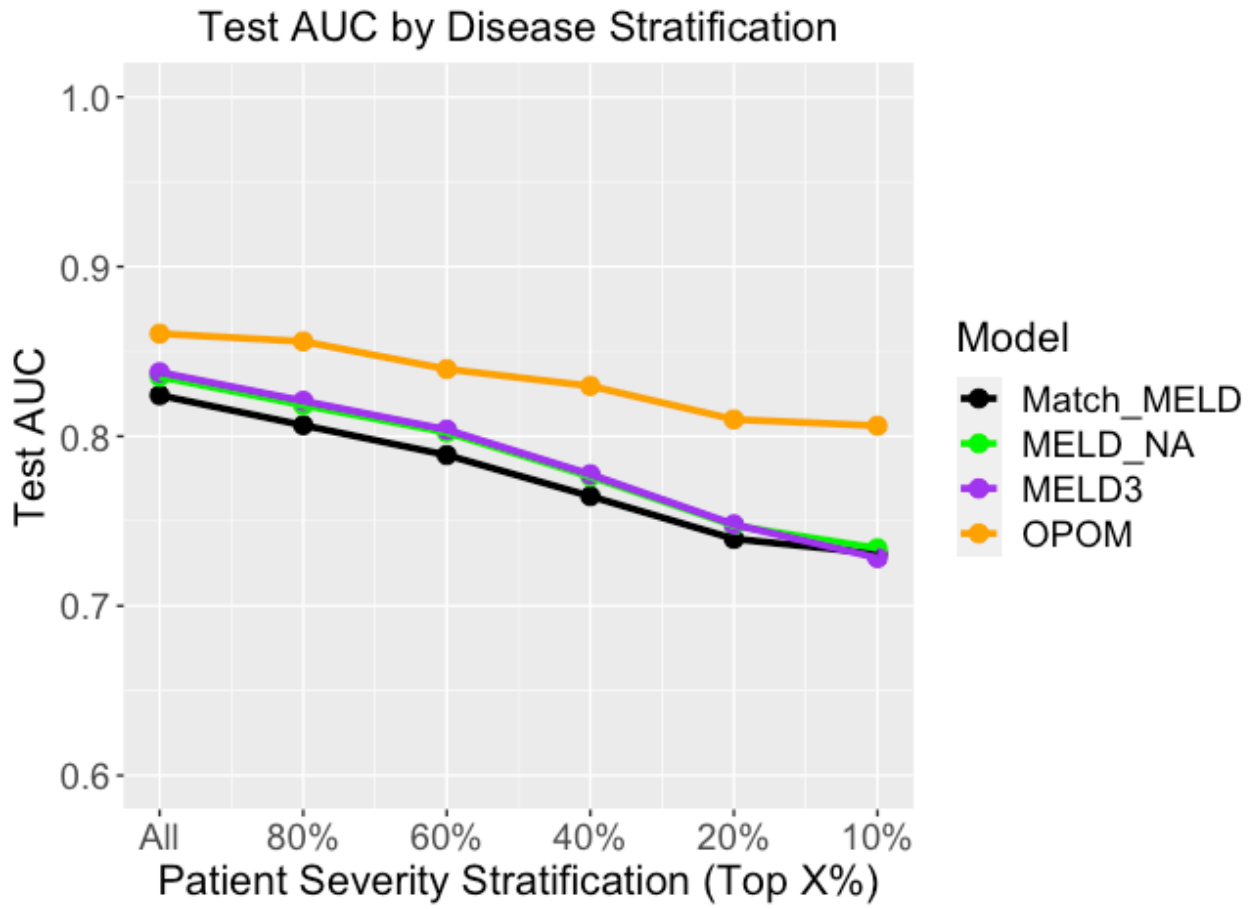
| | Variable name | | Variable name |
|---|---|---|---|
| 1 | Albumin level | 16 | Dialysis at previous check-in or not |
| 2 | Serum bilirubin | 17 | Change in bilirubin level since previous check-in |
| 3 | Serum creatinine | 18 | Change in creatinine level since previous check-in |
| 4 | INR | 19 | Change in INR since previous check-in |
| 5 | Serum sodium level | 20 | Change in albumin level since previous check-in |
| 6 | Dialysis in the last week or not | 21 | Change in sodium level since previous check-in |
| 7 | Number of years the candidate has accrued on the waitlist | 22 | Change in Lab MELD score since previous check-in |
| 8 | Age in years | 23 | Log of the candidate's bilirubin level |
| 9 | Lab MELD score provided by SRTR | 24 | Log of the candidate's creatinine level |
| 10 | Albumin level at previous check-in | 25 | Log of the candidate's INR |
| 11 | Serum bilirubin at previous check-in | 26 | AFP |
| 12 | Serum creatinine at previous check-in | 27 | Number of tumors |
| 13 | INR at previous check-in | 28 | Sum of size of tumors |
| 14 | Serum sodium at previous check-in | | |
| 15 | Lab MELD score at previous check-in | | |

28 variables examined, 20 associated with the traditional MELD, but in this instance applied with use of trends

HCC candidates: AFP, Tumor number/size



# Accuracy disease severity: MELD variants vs OPOM




The sicker your patient becomes, the less accurate MELD variants become

**With MELD, we are failing at the moment we need the best mortality prediction tool**

**OPOM maintains predictive accuracy even for our sickest patients**

# Continuous Distribution

REMOVE HARD BOUNDARIES, INCREASE FLEXIBILITY

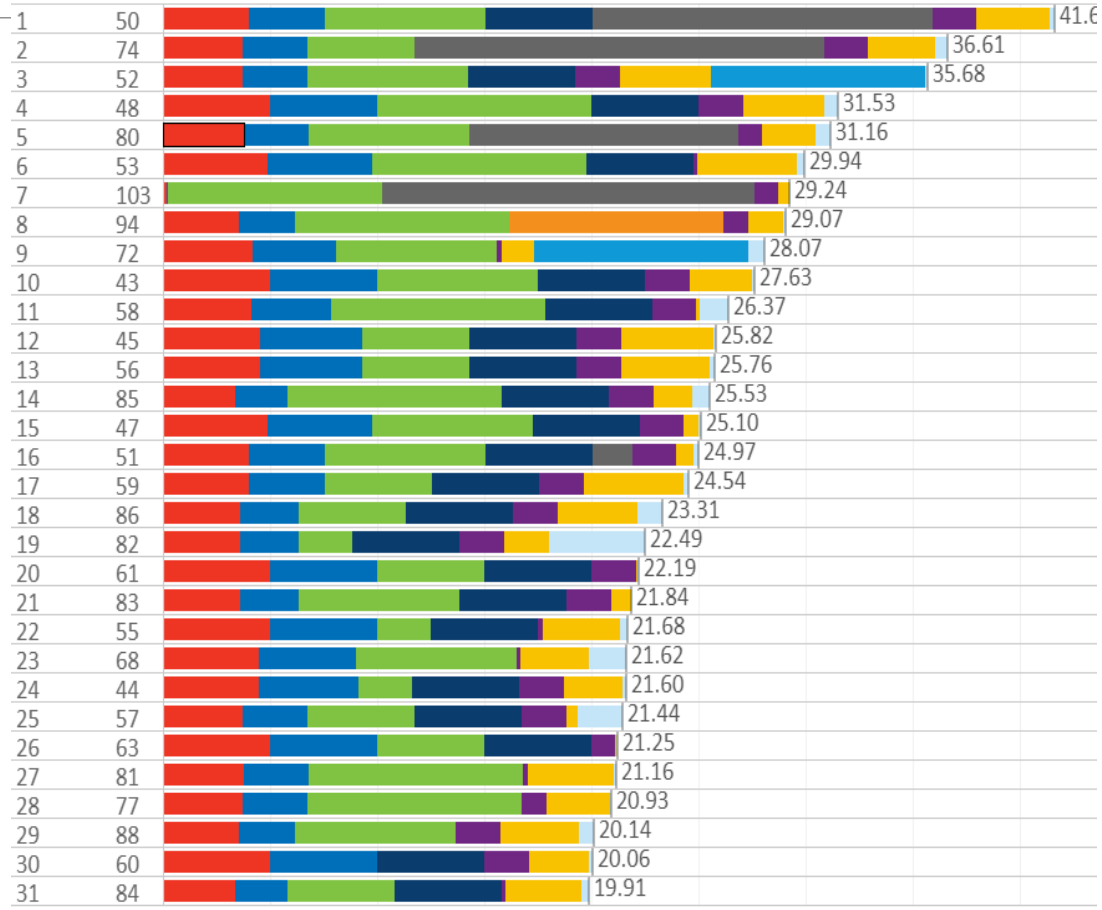
# Liver: Current State vs. Future State

## Classification Based System

**Table 9-11: Allocation of Livers from Non-DCD Deceased Donors at Least 18 Years Old and Less than 70 Years Old**

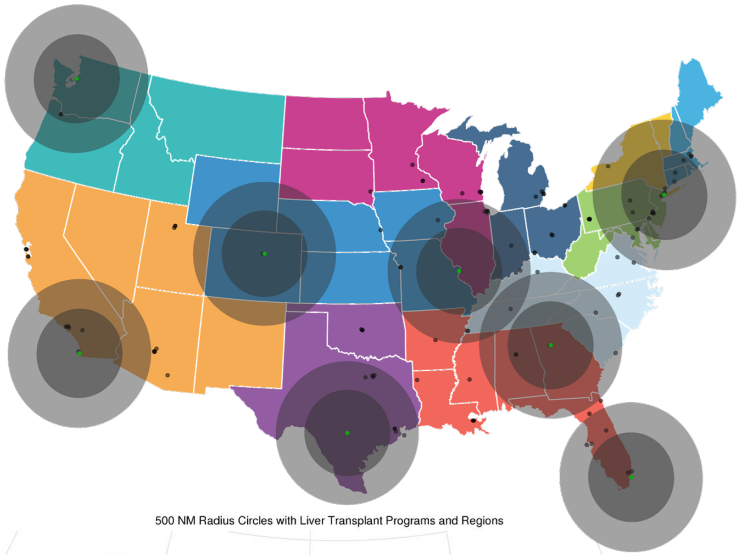
| Classification | Candidates with a MELD or PELD score of at least | And registered at a transplant hospital that is at or within this distance from a donor hospital | Donor blood type | Candidate blood type |
|---|---|---|---|---|
| 1 | Status 1A | 500NM | Any | Any |
| 2 | Status 1B | 500NM | Any | Any |
| 3 | Status 1A | 2,400NM and candidate is registered in Hawaii or 1,100NM and candidate is registered in Puerto Rico | Any | Any |
| 4 | Status 1B | 2,400NM and candidate is registered in Hawaii or 1,100NM and candidate is registered in Puerto Rico | Any | Any |
| 5 | 37 | 150NM | O | O or B |
| 6 | 37 | 150NM | Non-O | Any |

## Points Based System

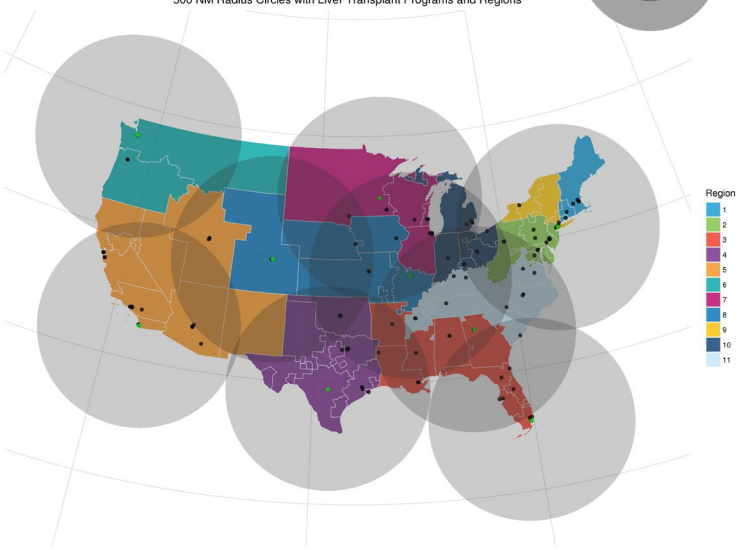


# “Acuity Circles” Priority Based on Nautical Miles (nm) from Donor Hospital (2/4/2020)

150nm
250nm




500nm




## Allocation Priority

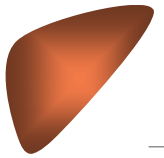
500nm: Status 1

150nm→250nm→500mn: MELDNa ≥ 37
150nm→250nm→500mn: MELDNa ≥ 33
150nm→250nm→500mn: MELDNa ≥ 29
150nm→250nm→500mn: MELDNa ≥ 15

National: Status 1
National: MELDNa ≥ 15

150nm→250nm→500mn: MELDNa <15

# Current Policy Allocation Policy (hard boundaries)



| | 150 | 250 | 500 | National |
|---|---|---|---|---|
| Status 1A | | | | |
| Status 1B | | | | |
| 37 or higher | | | | |
| 37 or higher | | | | |
| 37 or higher | | | | |
| 33-36 | | | | |
| 33-36 | | | | |
| 33-36 | | | | |
| 29-32 | | | | |
| 29-32 | | | | |
| 29-32 | | | | |
| 15-28 | | | | |
| 15-28 | | | | |
| 15-28 | | | | |
| Status 1A | | | | |
| Status 1B | | | | |
| 15-28 | | | | |
| Any | | | | |
| Any | | | | |
| Any | | | | |
| Any | | | | |

# Overview of Continuous Distribution

- Goal of continuous distribution is to **remove hard boundaries** between classifications that exist in the current allocation system
- Continuous distribution will result in:
  - Improved equity for candidates on the waitlist
  - Increased transparency in the allocation system
  - More potential for flexibility for future policy changes and implementation

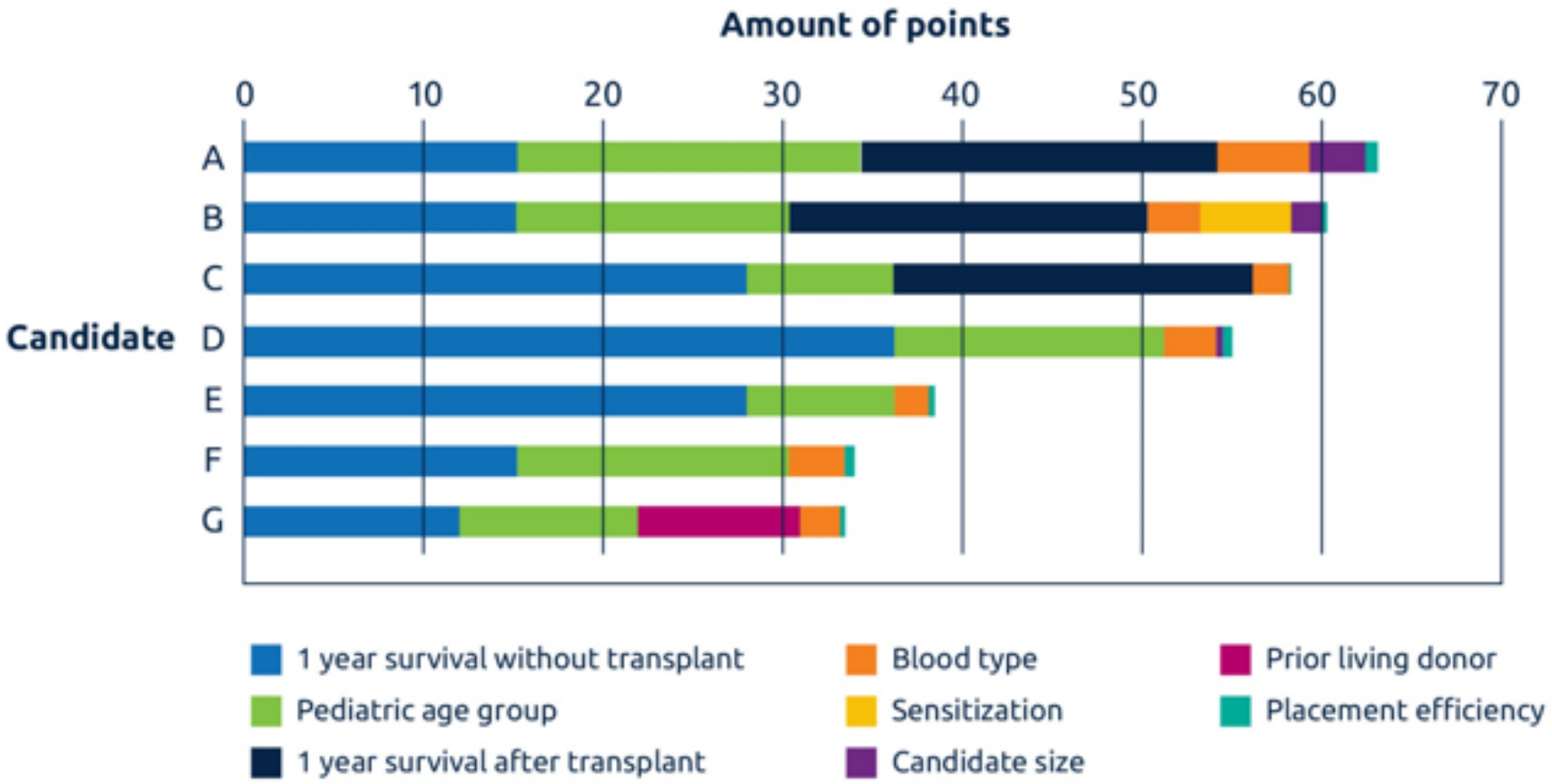
# Continuous Distribution: Composite Allocation Score

**Example** of weighted attributes


| 75% | 0% | 5% | 10% | 10% | 100% |
|---|---|---|---|---|---|

Every organ type will have its own unique formula with differently-weighted attributes.

# Composite Allocation Score (CAS)




Courtesy of UNOS

## Medical Urgency

Prioritizing medically urgent candidates

- Status 1A/1B
- MELD/PELD/OPOM
- Candidate diagnosis points (Status 1B)
- Liver-intestine registration

## Biological Disadvantages

Reducing biological disadvantages

- Candidate blood type
- Height/BSA

## Patient Access

Promoting patient access

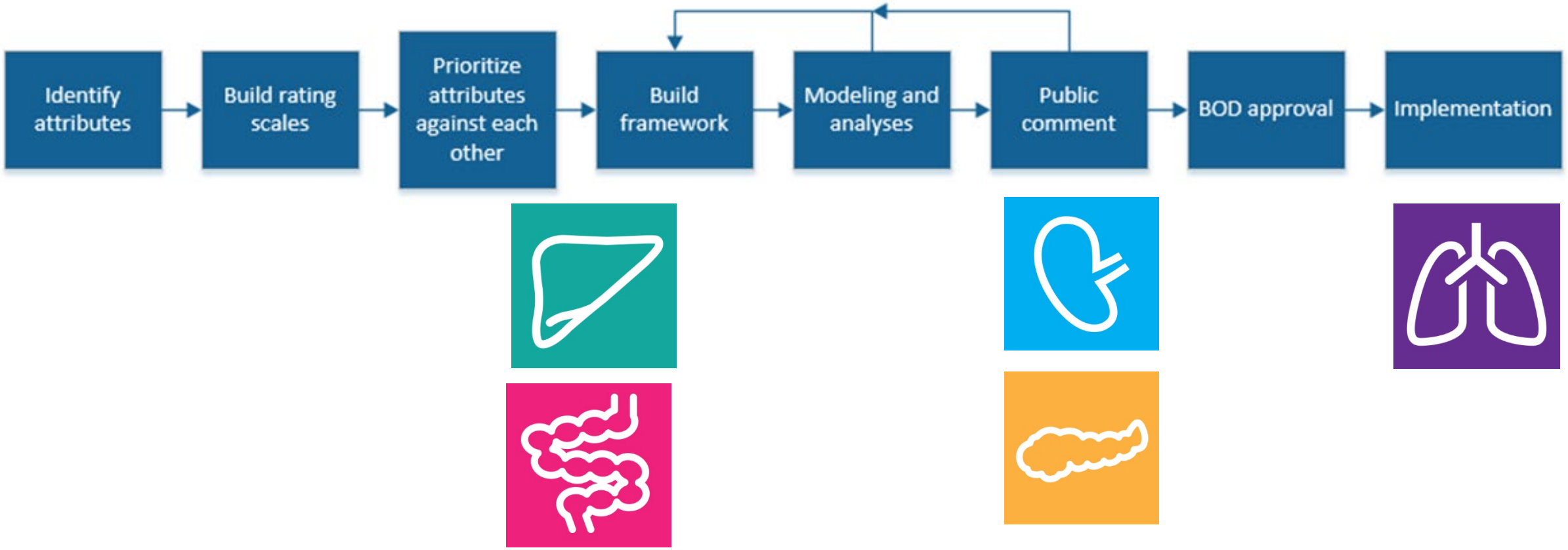
- Pediatric Priority
- Liver-intestine registration
- Prior living donor
- Split liver transplant
- Geographic Equity

## Placement Efficiency

Promoting the efficient management of the organ placement system

- Travel efficiency
- Proximity efficiency

# Steps to Continuous Distribution

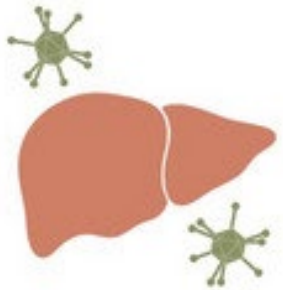


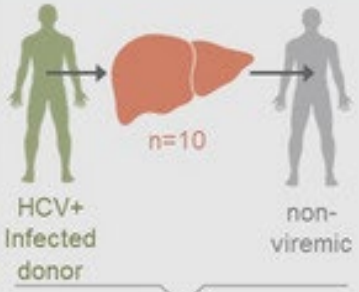
# Using and Improving Extended Criteria Donors

# Use of HCV Infected Liver Grafts

## Liver transplantation for hepatitis C virus (HCV) non-viremic recipients with HCV viremic donors

Does transplanting HCV-infected livers into non-viremic recipients impact outcomes?






monitored HCV level in blood

direct-acting antiviral therapy

All recipients:

derived Hepatitis C infection from donor

achieved sustained virologic response at 12 weeks posttreatment

no graft losses or death at 1 year posttransplant


Kwong et al

10.1111/ajt.15162 AJT

## Immediate administration of antiviral therapy after transplantation of hepatitis C-infected livers into uninfected recipients: Implications for therapeutic planning

Is immediate DAA therapy after transplant of a HCV-viremic liver to an HCV-uninfected recipient feasible and effective?


Open-label, unblinded, single-center study

10 HCV+ donor livers transplanted to HCV- recipients

12-week course of glecaprevir-pibrentasvir begun within 5 days post-Tx

RNA assays
Outcomes

100%
survival rate of graft and patients at a median of 46 weeks of follow-up

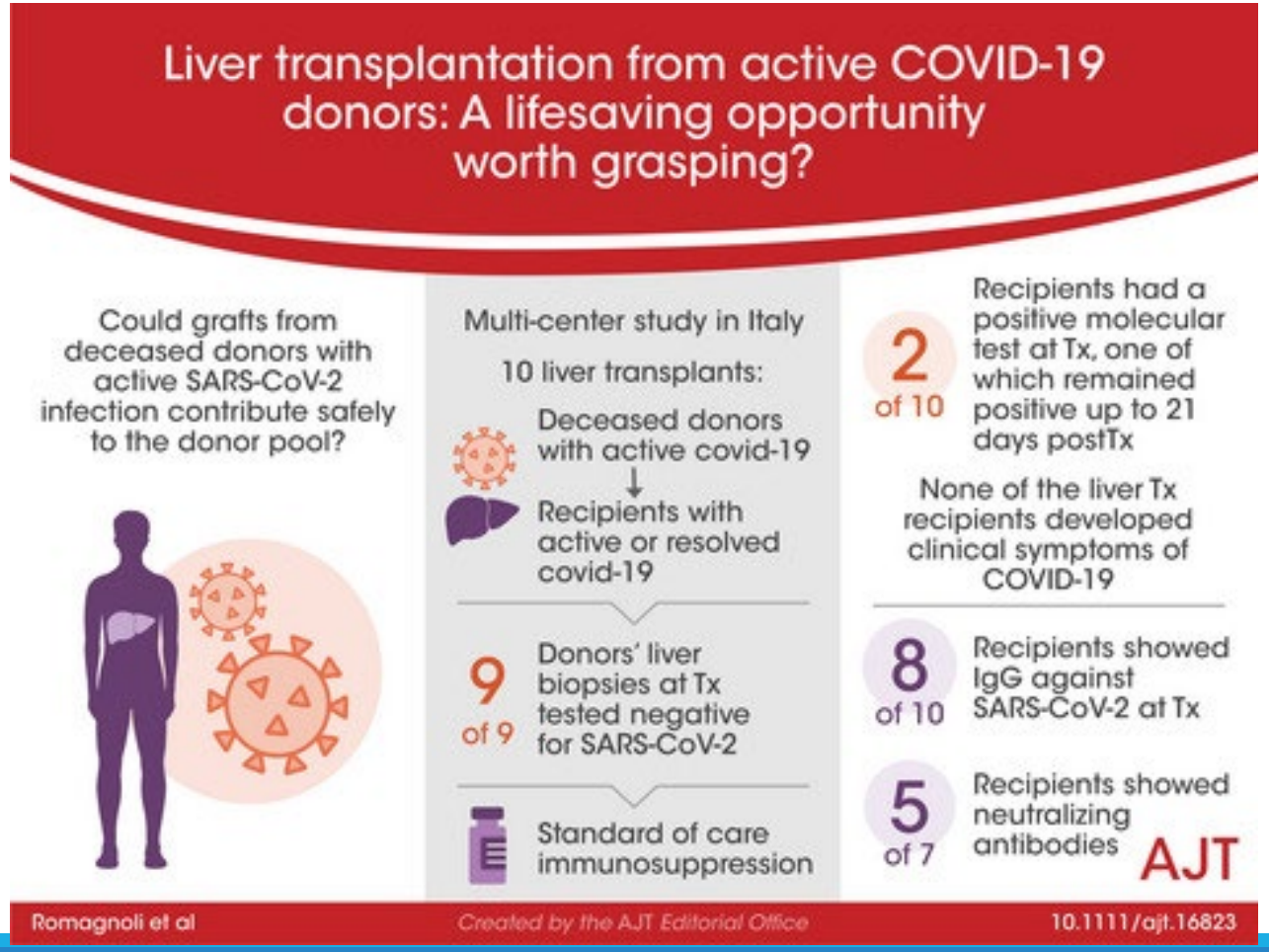
100%
of patients showed negative HCV RNA 12 weeks after completion of DAA therapy

No evidence
of DAA-associated hepatotoxicity

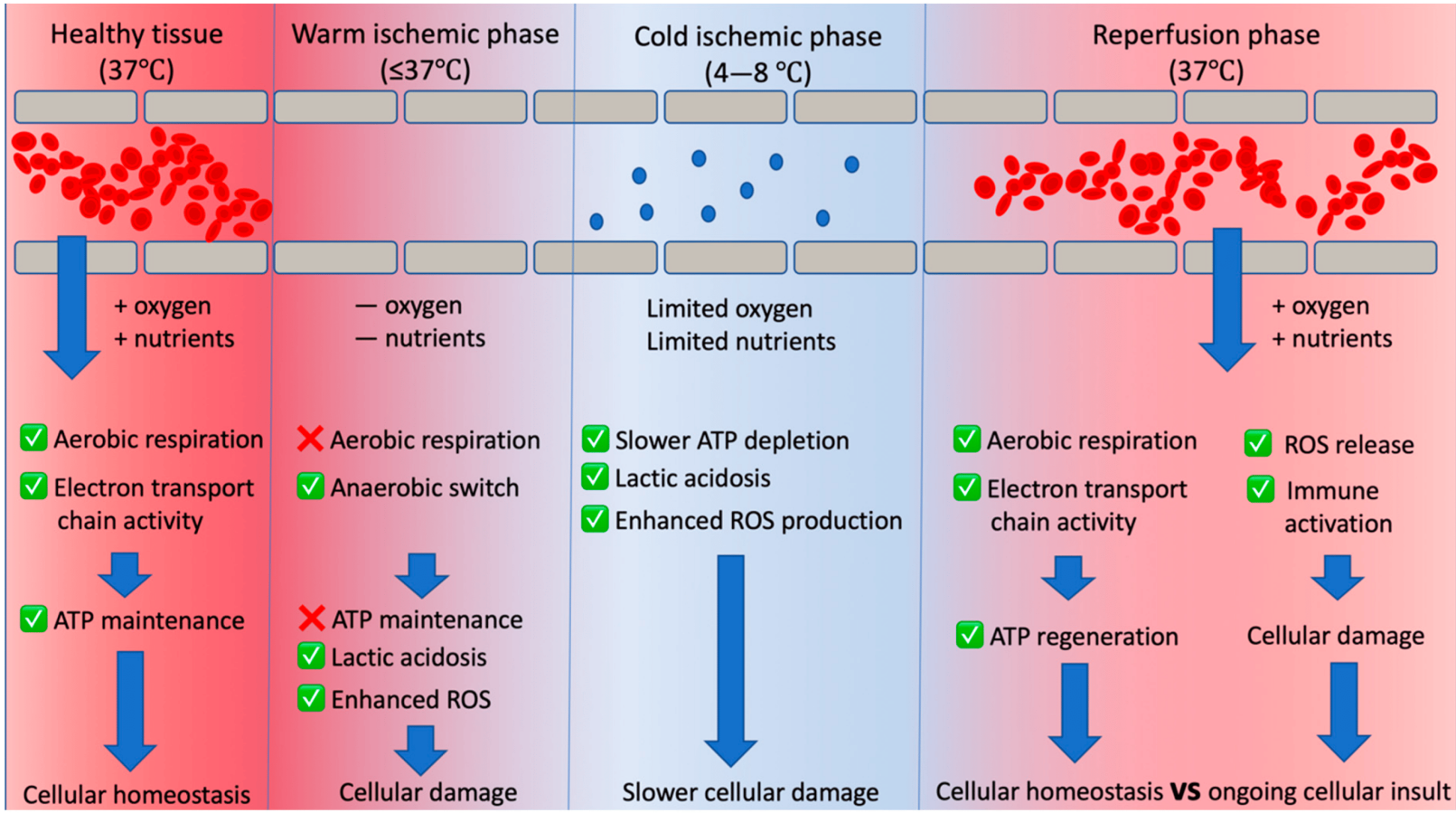
Bethea et al

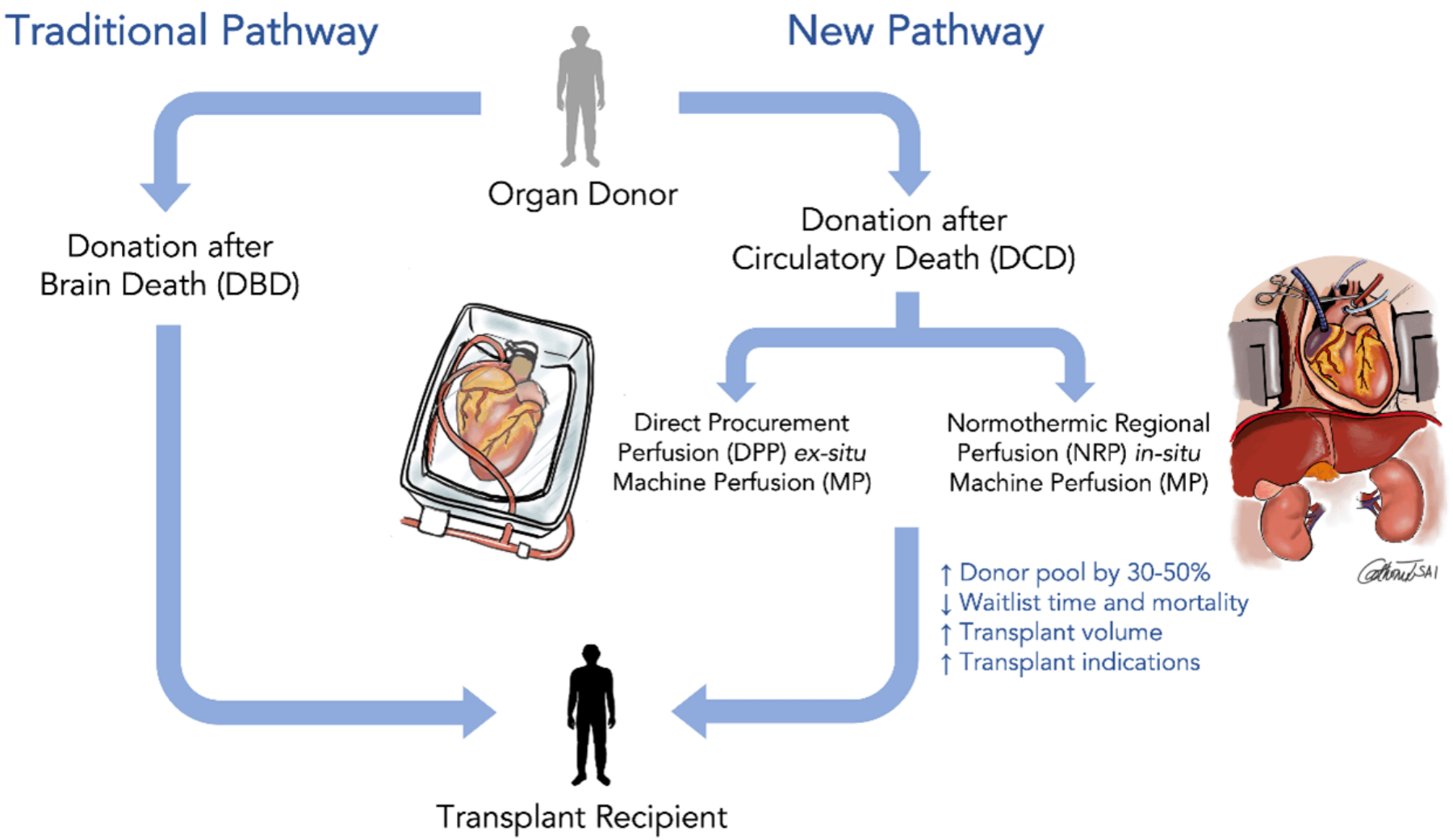
10.1111/ajt.15768 AJT

# Liver Grafts from COVID Infected Donors



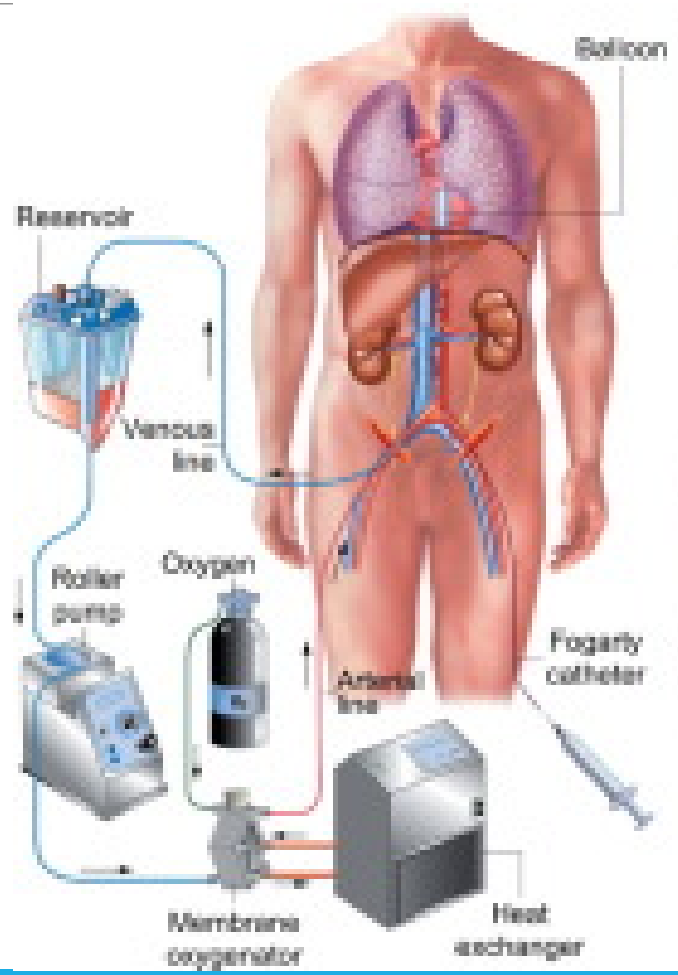
# ‘Liver Pumping’


Healthy tissue
(37°C)
Warm ischemic phase
(≤37°C)
Cold ischemic phase
(4—8 °C)
Reperfusion phase
(37°C)
+ oxygen
+ nutrients
— oxygen
— nutrients
Limited oxygen
Limited nutrients
+ oxygen
+ nutrients
Aerobic respiration
Electron transport chain activity
ATP maintenance
Cellular homeostasis
Aerobic respiration
Anaerobic switch
ATP maintenance
Lactic acidosis
Enhanced ROS
Cellular damage
Slower ATP depletion
Lactic acidosis
Enhanced ROS production
Slower cellular damage
Aerobic respiration
Electron transport chain activity
ATP regeneration
Cellular homeostasis VS ongoing cellular insult
ROS release
Immune activation
Cellular damage

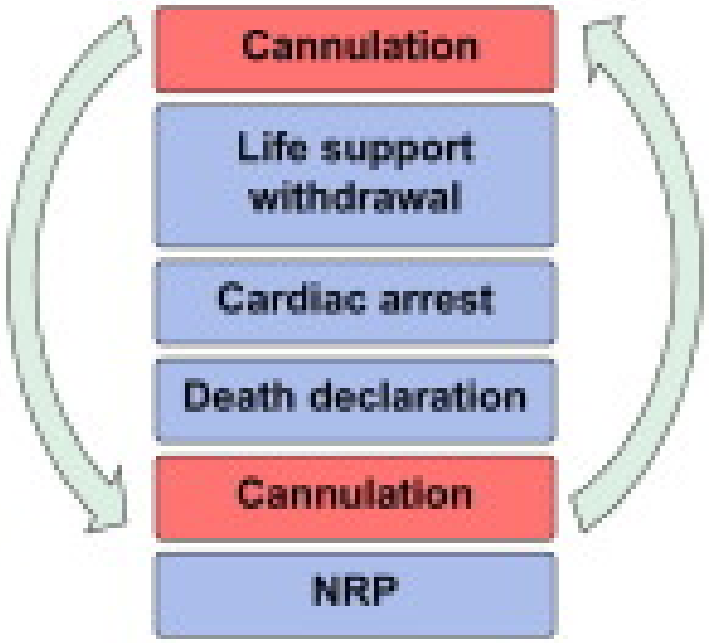

Traditional Pathway
New Pathway
Organ Donor
Donation after Brain Death (DBD)
Donation after Circulatory Death (DCD)
Direct Procurement Perfusion (DPP) ex-situ Machine Perfusion (MP)
Normothermic Regional Perfusion (NRP) in-situ Machine Perfusion (MP)
↑ Donor pool by 30-50%
↓ Waitlist time and mortality
↑ Transplant volume
↑ Transplant indications
Transplant Recipient

# Normothermic Machine Perfusion (NMP)

# Normothermic Regional Perfusion (NRP)



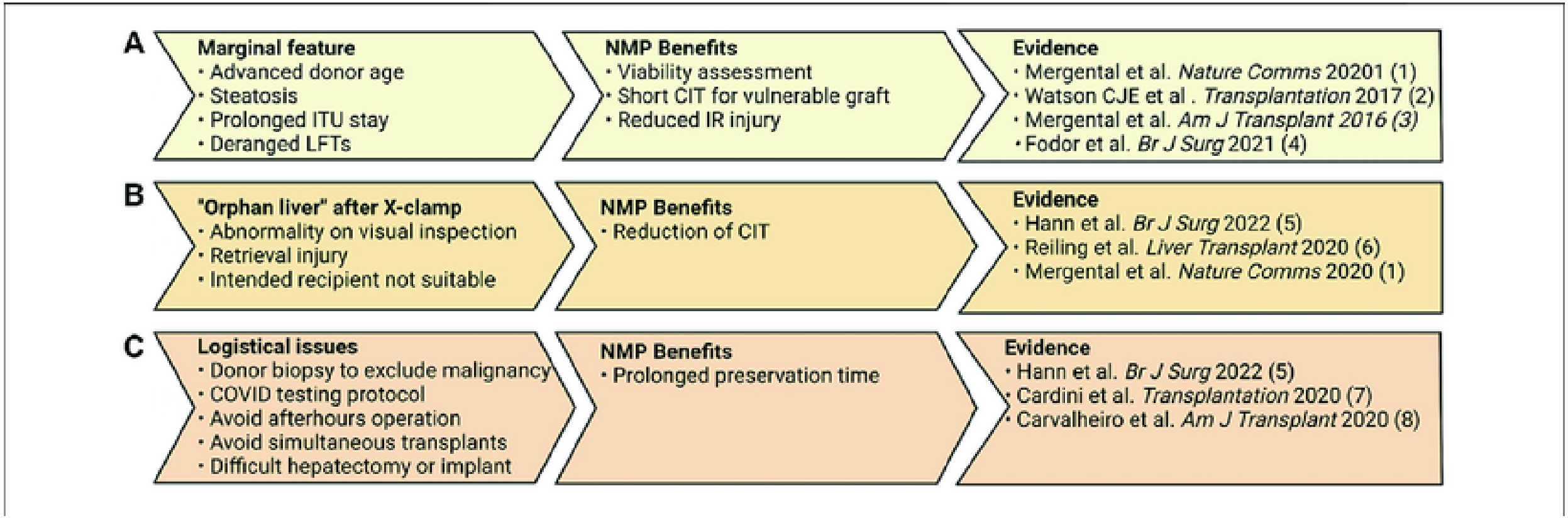

**cDCD liver transplantation performed with post-mortem normothermic regional liver transplantation:**




**Post-transplant outcomes *vs.* super rapid recovery:**

- Biliary complications:
  **8%** NRP *vs.* 31% SRR
- ITBL:
  **2%** NRP *vs.* 13% SRR
- Graft loss:
  **12%** NRP *vs.* 24% SRR

# Advantages of NRP



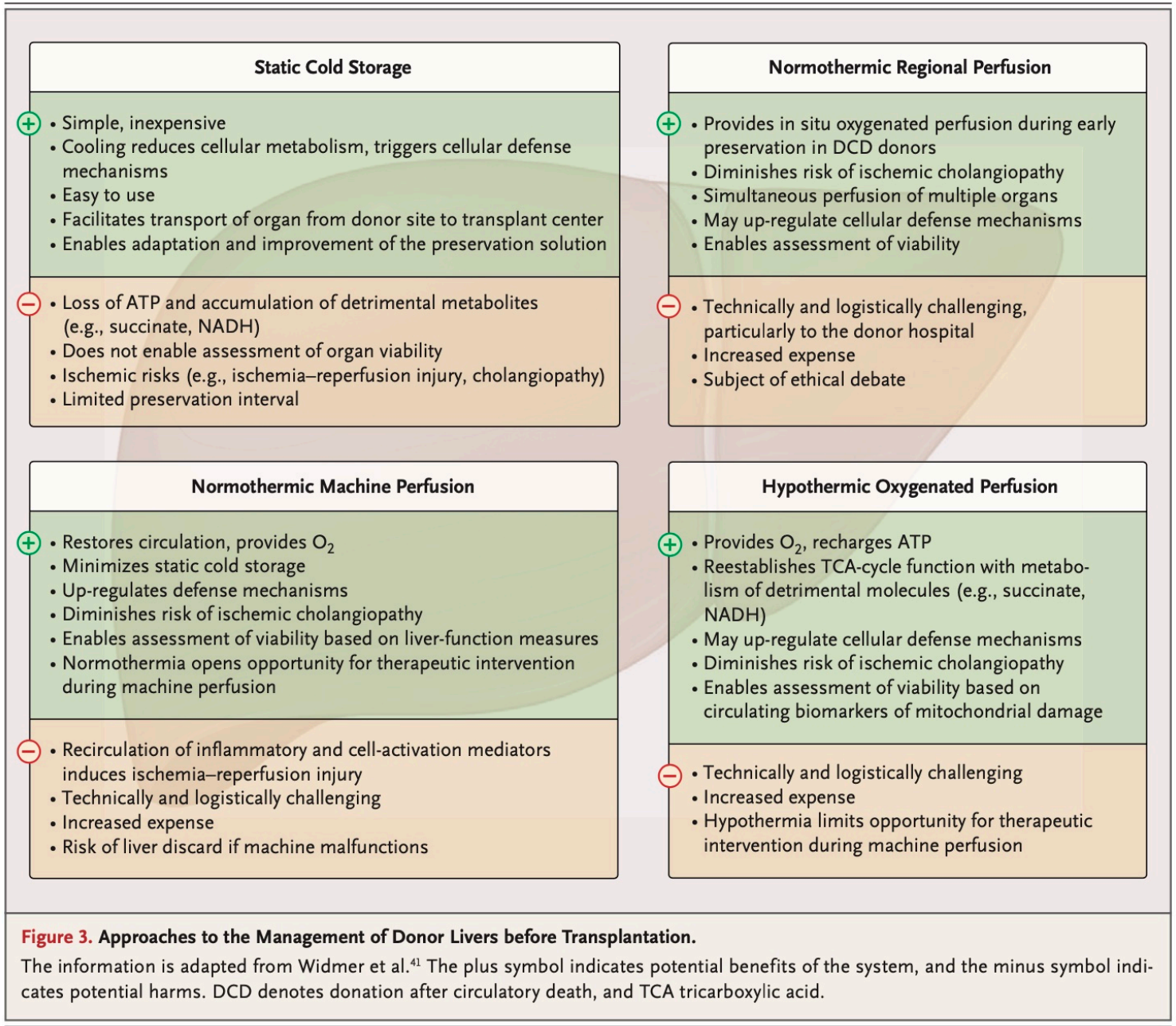



**Figure 3. Approaches to the Management of Donor Livers before Transplantation.**

The information is adapted from Widmer et al.[41] The plus symbol indicates potential benefits of the system, and the minus symbol indicates potential harms. DCD denotes donation after circulatory death, and TCA tricarboxylic acid.

# Take Home Points

- MELDNa → MELD 3.0 (July 2023)
- Future Allocation: Continuous Distribution
- Future MELD exceptions: iCRC mets, iCCA
- Expanding the Donor Pool: HCV, COVID, NMP, NRP